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Cardiovascular Disease

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Cardiovascular Disease
Funded Projects

Research Awards

Anderson, Steven E.	Na/H Exchange in Hypoxic/Ischemic Myocardium: Effects on Ca	University of California, Davis
Charo, Israel F.	Monocyte Chemoattractant Protein (MCP-1) in Atherosclerosis	Gladstone Foundation Laboratories
Curtiss, Linda K.	Functional Synthetic Peptide Mimics of Apolipoprotein E	The Scripps Research Institute
Fox, Joan E.	Regulation of GP IIb-IIIa by the Platelet Cytoskeleton	Children's Hospital Med. Ctr. of No. CA
Gonzalez-Cadavid, Nestor	Role of Nitric Oxide in Smoking-Related Vascular Impotence	REI, Inc, Harbor-UCLA Medical Center
Innerarity, Thomas L.	Cloning & Expression of the Apo-B mRNA Editing Factor	Gladstone Foundation Laboratories
O'Toole, Timothy E.	Integrin Cytoplasmic Domains and Ligand Affinity Modulation	The Scripps Research Institute
Parthasarathy, Sampath	Mechanisms Underlying Smoking-Induced Oxidation of LDL	University of California, San Diego
Pitas, Robert E.	Role of the Acetyl LDL Receptor in Atherogenesis	Gladstone Foundation Laboratories

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Smith, Jeffrey W.	Cell Adhesion Receptors in Atherogenesis	The Scripps Research Institute

IDEA Awards

Macey, Robert I.	Interaction of Cadmium with Sickle Red Cells	University of California, Berkeley
Ruoslahti, Erkki	The Role of TGF-B1 In Intimal Hyperplasia	La Jolla Cancer Research Foundation

2023470967

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Anderson, Steven E.

ABSTRACT

Na/H exchange in hypoxic/ischemic myocardium: effects on Ca

Title of Research Project (do not exceed 60 spaces)

Department of Human Physiology, University of California, Davis

Department and Institution

The objective of the proposed studies is to continue investigating the role of Na/H exchange in modulating intracellular Na, Ca, and H (Na_i, Ca_i, and H_i) in the heart during and after ischemia and hypoxia. This work will help us understand the basic processes leading to myocardial injury and cell death commonly associated with coronary artery disease. Particularly in the context of tobacco-related diseases, the successful completion of these studies will help reduce death and disability among tobacco users who experience episodes of myocardial ischemia.

The aim of these studies is to further test the general hypothesis that the sequence of events leading to hypoxic/ischemic cell damage is: 1) increased anaerobic metabolism → 2)increased H_i → 3) pH regulatory Na/H exchange → 4) increased Na_i → 5) decreased and/or reversed Na/Ca exchange → 6) increased Ca_i → 7) a cascade of Ca-dependent events leading to cell damage (i.e., stimulation of phospholipase, mitochondrial damage, unregulated protein phosphorylation, increased ATP consumption, superoxide generation, etc.) Early explanations for the mechanisms of myocardial dysfunction and cell death during and after ischemia commonly invoked a lack of available energy in the form of ATP. Although many investigators continue to hold that view, much new evidence has been consistent with the general hypothesis outlined above. This hypothesis predicts and is supported by recently reported results suggesting that, contrary to the commonly held view, increased Na_i (and Ca_i secondarily) causes an increase in myocardial energy consumption early during hypoxia/ischemia and that these effects can be inhibited by Na/H exchange blockers. Much evidence supporting the hypothesis, however, was from isolated cells or depended upon interpretation of changes in H_i and/or contractility in response to inhibitors which may not be specific for Na/H exchange.

In order to better characterize the relevant transport and pathways, we will test the hypothesis in the intact organ by measuring changes in each of the ions after altering the stimuli or the forces which determine ion transport. This will include experiments designed to quantify the extent to which other pathways such as Na+K+2Cl and Na and Ca channels contribute to changes in Na_i and Ca_i during and after hypoxia/ischemia. In addition, after testing the specificity of pharmacological interventions we will use them to further characterize the transport pathways as well as measure their efficacy in decreasing Na and Ca accumulation in order to limit myocardial injury. The hypothesis will be tested in isolated perfused rabbit hearts using 23Na, 31P, and 19F NMR to measure changes in Na_i and cell volume, H_i and high energy phosphates, and Ca_i respectively. Myocardial contractility will be continuously measured by a left ventricular balloon. The "NH_4Cl prepulse", osmotic insults, and hypoxia and ischemia followed by reoxygenation and reperfusion will be used to investigate the stimuli(us) for increased Na_i and Ca_i. Manipulations of intra- and extracellular ion concentrations will be used to alter the driving forces for Na, H, and Ca transport and thus unambiguously identify the pathways operating in response to the stimuli.

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Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Charo, Israel F.

ABSTRACT

Monocyte Chemoattractant Protein (MCP-1) in Atherosclerosis

Title of Research Project (do not exceed 60 spaces)

Gladstone Institute of Cardiovascular Disease

Department and Institution

The overall goal of this grant is to address the role of the monocyte chemoattractant protein MCP-1 in fatty-streak formation in atherosclerosis. A prominent feature of early atherosclerotic lesions is the accumulation of lipid-laden macrophages, known as foam cells, in the subendothelium of arterial walls. Recent data indicate that circulating monocytes are the precursors of these foam cells. Foam cell formation requires the directed migration of monocytes toward the subendothelium in response to a chemotactic gradient, followed by activation of cellular receptors that mediate the attachment of monocytes to endothelial cells and matrix proteins in the subendothelium. The studies proposed in this application will investigate the potential role of the monocyte-specific chemoattractant protein MCP-1 in mediating monocyte adhesion and migration into the subendothelium. Experiments will be performed to determine whether adhesion receptors on monocytes are up-regulated or otherwise activated by MCP-1, and to determine which of these may be involved in mediating monocyte adhesion in response to MCP-1. Because the receptor-binding domain(s) of MCP-1 is unknown, a major focus of this application will be the identification of this region(s) through the use of monoclonal antibodies, synthetic peptides, and the creation of chimeric proteins between MCP-1 and the homologous neutrophil-specific chemoattractant IL-8. Recombinant MCP-1/IL-8 will be expressed in mammalian cells and bacteria. Definitive experiments to determine whether MCP-1 is important in foam cell formation *in vivo* require species-specific reagents, and these will be developed for use in the rabbit. Rabbits will be maintained on a high-fat, high-cholesterol diet, and MCP-1 synthesis in cells of the aorta will be determined by *in situ* hybridization and immunocytochemistry, and compared with that in rabbits on a control diet. Monoclonal antibodies to rabbit MCP-1 will be used *in vivo* to determine whether this cytokine plays an important role in foam cell formation in the hypercholesterolemic rabbit. The proposed research should increase our knowledge of the molecular mechanisms of monocyte-endothelial cell interactions in response to MCP-1, and may form a basis for the design of rational and novel strategies to prevent the initiation of atherosclerosis.

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Principal Investigator: Linda K. Curtiss, Ph.D.

ABSTRACT

FUNCTIONAL SYNTHETIC PEPTIDE MIMICS OF APOLIPOPROTEIN E

Title of Research Project (do not exceed 60 spaces)

Immunology, The Scripps Research Institute

Department and Institution

Cigarette smoking is one of the major risk factors for coronary and peripheral vascular disease. Nicotine and carbon monoxide, products of cigarette smoking, contribute to the atherosclerotic process. Furthermore, users of tobacco have 2.5 times the prevalence of hypercholesterolemia compared to nonsmokers. This elevated blood cholesterol further increases the risk for the development of cardiovascular disease. Cholesterol is transported by cholesterol-rich lipoproteins that contain apolipoproteins (apo) B-100 and E. Both apo B and apo E bind to the low density lipoprotein (LDL) receptor, but hepatic LDL receptors are down-regulated by high blood cholesterol. Hepatic chylomicron remanent receptors are not down-regulated and can therefore be used to enhance the hepatic removal of cholesterol-rich particles if those lipoproteins contain apo E. A recently identified candidate for the apo E-binding remnant receptor is the LDL receptor related protein or LRP. We have recently demonstrated that a lipid-free synthetic peptide, which contains apo E amino acid residues 141-155 repeated twice in tandem, binds the LDL receptor. Because LRP contains reiterated LDL-like ligand binding domains, the probability is strong that the dimeric peptide also binds LRP. By promoting the association of the apo E peptide with cholesterol-rich lipoproteins we predict that their hepatic uptake can be enhanced. There are 4 specific aims: The first is to optimize the lipid-binding properties of the dimeric apo E peptide. The second is to verify that our lipoprotein-bound synthetic peptide binds LRP. The third is to optimize the structure of the peptide for high affinity chylomicron remnant receptor and/or LRP binding, and the final aim is to begin to test the effectiveness of the synthetic peptide mimic in lowering blood cholesterol *in vivo*. In the process of achieving this goal, much valuable information will be gained regarding structural requirements for the participation of apo E-specific lipoproteins in regulating cholesterol. Furthermore, these synthetic peptides, through lowering of the circulating levels of the atherogenic lipoproteins, may provide a therapeutic intervention for reducing or reversing the long term effects of tobacco use.

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Principal Investigator: Fox, Joan E. B.

ABSTRACT

Regulation of GP IIb-IIIa by the platelet cytoskeleton

Title of Research Project (do not exceed 60 spaces)

Gladstone Institute of Cardiovascular Disease

Department and Institution

Cigarette smoking leads to increased adhesion of blood cells to the vessel wall and increased aggregation of platelets. These events are mediated by members of the integrin superfamily of transmembrane receptors. While many receptors for adhesive molecules are constitutively active, several integrins can be rapidly and reversibly activated. The glycoprotein (GP) IIb-IIIa complex on platelets is such an integrin. On unstimulated cells, the complex cannot bind fibrinogen. On activated cells, the complex undergoes a change that allows it to bind fibrinogen and thus to induce platelet aggregation. Little is known about the mechanisms that induce activation of GP IIb-IIIa or of integrins in other blood cells. Because integrins can associate with the cytoskeleton in cultured cells, many investigators have suggested that the cytoskeleton may regulate the functional state of these receptors. However, it has been difficult to demonstrate an association of integrins with the cytoskeleton in unstimulated blood cells. Recently, we showed that this difficulty may result from the use of inappropriate lysis and sedimentation conditions. We have now established conditions for isolating a submembranous skeleton from platelets and have shown that a subpopulation of GP IIb-IIIa complex is associated with this structure. In preliminary studies, we have shown that $pp60^{c\text{-}src}$ is associated with the integrin-rich skeletal structure, additional signaling molecules (protein kinase C and phosphoinositide 3-kinase) associate with the skeletal structure upon platelet activation, and components of the skeleton become phosphorylated in the activated cell. Further, we have found that under the conditions used for our experiments, in which only a subpopulation of the GP IIb-IIIa complex is associated with the membrane skeleton, only a subpopulation of GP IIb-IIIa becomes functional in activated cells. The functional GP IIb-IIIa is pulled toward the center of the platelet, whereas the rest of the GP IIb-IIIa remains in filopodia and at the periphery of the cell. These findings have led us to hypothesize that the membrane skeleton plays a role in mediating activation of the GP IIb-IIIa complex, perhaps by localizing signaling molecules at sites of penetration of the integrin through the lipid bilayer. The proposed studies will test the hypothesis that the association of the GP IIb-IIIa complex with the membrane skeleton is needed for the complex to become activated. Experiments described in this proposal are designed 1) to identify the skeletal protein(s) with which the GP IIb-IIIa complex associates; 2) to characterize the domain on the GP IIb-IIIa complex that associates with the skeletal protein(s); 3) to test the hypothesis that the association of the GP IIb-IIIa complex with the membrane skeleton is of critical importance in allowing GP IIb-IIIa to become activated. It is anticipated that these studies will elucidate the way in which GP IIb-IIIa associates with the cytoskeleton and will shed light on mechanisms regulating the function of the complex in platelets. They should also increase our understanding of the function of integrin-cytoskeletal interactions in regulating other adhesive interactions in the vasculature.

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Gonzalez-Cadavid, Nestor F

Principal Investigator

ABSTRACT

ROLE OF NITRIC OXIDE IN SMOKING-RELATED VASCULAR IMPOTENCE

Title of Research Project (do not exceed 60 spaces)

RESEARCH AND EDUCATION INSTITUTE, INC.

DEPARTMENT OF SURGERY, DIV OF UROLOGY, HARBOR/UCLA MEDICAL CENTER

Department and Institution

Cigarette smoking has been identified statistically and experimentally as an important risk factor for the development of vasculogenic impotence. This disease is due to impairment of the penile corpora cavernosal smooth muscle relaxation triggered by the neurotransmission elicited by erotic stimuli. As a consequence erectile dysfunction, particularly in the presence of additional risk factors such as atherosclerosis, hypertension or diabetes, often results. It has recently been shown that penile erection is mediated by nitric oxide (NO) through a endothelial-smooth muscle interaction. The enzyme responsible for the synthesis of this compound, nitric oxide synthase (NOS), is present in both the smooth muscle and the endothelium of the corpora cavernosa. Considering that the effects of smoking and nicotine are mainly derived from a norepinephrine-like vasoconstrictor mechanism superimposed on various degrees of smooth muscle/endothelial damage, this project aims to determine in a rat model whether smoking impairs the NO-mediated relaxation mechanism in the penis, and if so which steps are affected and how could they be compensated. In vitro cultures of smooth muscle cells and endothelial cells from the corpora cavernosa will be used to assess the effects of nicotine, cotinine and/or an aqueous extract of cigarette smoke on NOS constitutive and inducible activities, synthesis and turnover. The release of nitrites, the stimulation of cGMP synthesis, and the uptake of Ca^{2+}, under putative agonists of the NANC response will be studied to examine tobacco-interference with other steps in the NO-related cascade. NOS mRNA levels will be determined upon induction with bacterial LPS, and the isozyme will be purified from the penile smooth muscle cells and its cDNA cloned. The effects of smoking and nicotine in vivo on the apomorphine-induced erectile response in rats submitted to additional risk factors for erectile dysfunction such as age or diabetes will also be investigated. The experimental increase of NOS levels in the corpora cavernosa by LPS injection will be performed to attempt to counteract the tobacco-induced damage on the penile relaxation process irrrespective on whether or not this occurs via the NO cascade.

2023470972

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Principal Investigator: Innerarity, Thomas L.

ABSTRACT

Cloning and Expression of the Apo-B mRNA Editing Factor

Title of Research Project (do not exceed 60 spaces)

Gladstone Institute of Cardiovascular Disease

Department and Institution

Apolipoprotein (apo-) B has a central role in lipoprotein metabolism, and apo-B-containing lipoproteins are known to be atherogenic. Apolipoprotein B48, which is essential for the assembly of chylomicrons in the intestine, is produced by a novel physiological process involving mRNA editing. Apolipoprotein B mRNA is modified so that the C at nucleotide 6666 is converted or exchanged for a U, creating an in-frame stop codon (UAA) that replaces the Gln codon (CAA). As a consequence, apo-B48 is synthesized instead of apo-B100. The mechanism for apo-B mRNA editing still remains to be clarified, and that is the goal of this application. An *in vitro* assay for apo-B mRNA editing has been established in our laboratory and has been used to characterize the apo-B mRNA editing activity from rabbit enterocytes. The characteristics of the editing reaction indicate that it is catalyzed by a nucleotide sequence-specific cytidine deaminase that is either a single protein or a multimeric protein that will be amenable to isolation by enzyme purification procedures. An *in vitro* assay for editing, along with fast protein liquid chromatography, high-pressure liquid chromatography, and other protein purification procedures, will be used to isolate the editing factor. We have now partially purified the editing factor, and the main objective of this proposal is to purify it to homogeneity. After the protein is purified to apparent homogeneity, partial amino acid sequences from the amino terminus and tryptic or CNBr fragments will be obtained in order to design appropriate oligonucleotide probes to screen a rabbit enterocyte cDNA library. The amino acid sequence will be deduced from the DNA sequence of overlapping cDNA clones. A full-length cDNA clone will be expressed to demonstrate apo-B mRNA editing activity. To characterize the apo-B mRNA editing, monoclonal and polyclonal antibodies to the apo-B mRNA editing factors will be produced and used to localize the sites of cellular and subcellular editing. In addition, antibodies will be useful reagents for determining the domain structure of the protein and the details of its interaction with apo-B mRNA. The apo-B mRNA editing is the first form of RNA editing described in mammalian cells, and the elucidation of this mechanism at a molecular level will yield valuable information for understanding not only apo-B synthesis, but also a unique form of RNA processing.

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Principal Investigator: O'Toole, Timothy E.

ABSTRACT

Integrin Cytoplasmic Domains and Ligand Affinity Modulation

Title of Research Project (do not exceed 60 spaces)

The Committee on Vascular Biology, The Scripps Research Institute

Department and Institution

Cardiovascular disease is one major consequence of excessive tobacco use. Extensive vessel wall damage can potentially result in thrombus formation leading to heart attack or stroke. Regulation of platelet function, therefore, is a main focus of antithrombotic therapy. The platelet membrane glycoprotein GPIIb-IIIa ($\alpha_{IIb}\beta_3$) is a member of the integrin family of cell adhesion receptors and is critically involved in the platelet aggregation response following vascular injury. The ability of $\alpha_{IIb}\beta_3$ to bind fibrinogen and inititate aggregation (to become "activated") is regulated in a specific and dynamic manner by extracellular agonists. While the precise intracellular signalling pathways used by such agonists remain unclear, G proteins, phospholipid metabolism, Ca^{2+} mobilization, and protein kinases have all been suggested to play a role. The cytoplasmic domains of integrin subunits are available to intracellular messenger systems and likely represent possible means of inside-out signal transduction. In our previous work, we have demonstrated that mutations of the cytoplasmic domain of the α_{IIb} subunit can change the ligand binding affinity of integrin $\alpha_{IIb}\beta_3$. We propose to test the hypothesis that specific integrin cytoplasmic domain sequences control the conformation and ligand binding affinity of the extracellular domain. Truncations and amino acid substitutions in the cytoplasmic domains of α_{IIb} and β_3 will be generated by standard mutagenesis procedures and the constructs co-expressed in Chinese hamster ovary (CHO) cells. Ligand binding affinity will be analyzed by the binding of conformation-specific monoclonal antibodies or adhesive ligands. In addition, we will analyze the affinity state of integrin chimeras constructed by joining α_{IIb} and β_3 with the cytoplasmic tails of other integrin subunits. We will also examine the possibility of cell or protein-specific regulators of integrin affinity. The wild type, truncated, or chimeric integrins discussed above will be transfected into a variety of cell lines and their ligand affinity state analyzed. Finally, we will investigate the role of α and β cytoplasmic sequences in three cellular postoccupancy events: spreading, focal contact formation, and stimulation of the Na^+/H^+ antiporter. These studies should localize precise integrin sequences and implicate transduction events or cellular factors involved in receptor activation and receptor function. This information may be useful in identifying novel therapeutic targets for unregulated or abnormal platelet aggregation and vascular disease.

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Principal Investigator: Parthasarathy, Sampath

ABSTRACT

Mechanisms Underlying Smoking-Induced Oxidation of LDL

Title of Research Project (do not exceed 60 spaces)

Department of Medicine, University of California, San Diego

Department and Institution

Cigarette smoking is one of the major risk factors for atherosclerosis and coronary heart disease, but the precise mechanisms remain uncertain. With the emergence of the oxidative modification hypothesis of atherogenesis, implicating free radical oxidation of low density lipoprotein (LDL) as a causative factor, there has been increasing attention to the possibility that the impact of cigarette smoking on coronary heart disease is related to this oxidative process. Cigarette smoking can acutely alter LDL in such a way that it becomes much more susceptible to oxidation *in vitro*, and this effect is inhibited strongly by prior intake of supplemental vitamin C or vitamin E. Exactly how cigarette smoking exerts these prooxidant effects, however, is unknown. While cigarette smoke does contain some long-lived free radicals, it seems unlikely that the oxidation of LDL occurs within the plasma. Plasma contains a very high concentration of a number of antioxidants and it is difficult to oxidize LDL in the presence of even low concentrations of plasma proteins. We wish to test an alternative hypothesis, namely, that the initial targets for oxidation are lipid components of cells. We propose that the oxidized lipids from cell membranes then exchange with or transfer to lipoprotein particles in the plasma. In other words, the cells directly exposed to smoke (macrophages, neurophils, alveolar epithelial cells or capillary endothelial cells) interact first with free radicals and/or other prooxidants. Alternatively (or in addition) cigarette smoke components may activate pro-oxidative systems within these cells (e.g., 15-lipoxygenase or NADPH oxidase) and thus increase their endogenous rate of generation of lipoperoxides. Because hydroperoxides of fatty acids are relatively stable, they can be regarded as a mechanism for "transporting" a high oxidative potential from the alveolus to the interface between endothelial cells and plasma. While a good deal is known about the normal function of lipid transfer proteins, surprisingly little research has been done on transfer of oxidized lipids. In the first phase of our study, we propose to test whether lipid peroxides and other oxidized lipids do transfer from cells to lipoproteins and whether one or more of the several known lipid transfer proteins can accelerate the process. We will also test whether cigarette smoke (or components thereof) activate cultured lung-derived cells with respect to their ability to oxidatively modify LDL (e.g., by enhancing lipoxygenase or NADPH oxidase activity). These first phase studies will be done using well-defined cell culture systems. The results obtained will allow us to design optimally the second phase studies utilizing perfused lungs. The relative importance of the several possible mechanisms can be evaluated readily by controlling the composition of the perfusion medium (e.g., by including inhibitors of lipoxygenase) or by examining the lung tissue directly (e.g., for changes in lipoxygenase or NADPH oxidase induced by smoking or by examining the tissue for the nature of the lipid oxidation products generated).

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Principal Investigator: Pitas, Robert E.

ABSTRACT

Role of the Acetyl LDL Receptor in Atherogenesis

Title of Research Project (do not exceed 60 spaces)

Gladstone Institute of Cardiovascular Disease

Department and Institution

The mechanisms by which cigarette smoking and elevated plasma low density lipoprotein (LDL) levels lead to an increased risk of cardiovascular disease and to accumulation of lipid in cells of the arterial wall are largely unknown. It is our long-term objective to understand these mechanisms. Data from both *in vitro* and *in vivo* experiments suggest that the uptake of oxidized LDL by the acetyl LDL, or scavenger, receptor is important in the pathogenesis of atherosclerosis and contributes to the formation of foam cells of macrophage and smooth muscle cell (SMC) origin. We have demonstrated that platelet secretory products up-regulate acetyl LDL receptor expression by SMC. The first specific aim of this project is to study the regulation of acetyl LDL receptor expression in SMC. We will identify the factors present in platelet secretory products and in tissue extracts that regulate acetyl LDL receptor expression; determine whether activation of protein kinase C up-regulates receptor expression; and determine the mechanism of regulation (i.e., transcription, translation, or receptor activation) that leads to the increase in receptor activity induced by phorbol esters and platelet-derived secretory products. The second major goal of this project is to determine the role of the acetyl LDL receptor in the pathogenesis of atherosclerosis. To accomplish this, we will produce transgenic mice with altered receptor expression in macrophages or SMC by expressing mutant forms of the receptor that will combine with native receptor monomers to form inactive heterotrimers. Even in the presence of native receptor protein, the mutant forms will act as dominant negative mutations to produce cells with a receptor-negative phenotype in heterozygous animals. As a second specific aim, we will produce mutant forms of the acetyl LDL receptor and screen for dominant negative forms of the receptor in cells in culture. As a third specific aim, we will produce transgenic animals that overexpress the native acetyl LDL receptor or express dominant negative mutations of the receptor. We will produce and test constructs for expression under the control of hepatocyte-, SMC-, or macrophage-specific promoters, and express the constructs in transgenic animals. The animals will express the native receptor in hepatocytes, SMC, and macrophages. Expression of the dominant negative mutants will lead to loss of expression of receptor activity in macrophages and SMC. As a fourth specific aim, we will use these transgenic animals to determine the effect of alterations in acetyl LDL receptor expression on diet-induced atherogenesis.

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Principal Investigator: Smith, Jeffrey W.

ABSTRACT

A Cell Adhesion Receptor In Atherogenesis

Title of Research Project (do not exceed 60 spaces)

Committee on Vascular Biology, The Scripps Research Institute

Department and Institution

Atherosclerosis is one of the leading causes of death in the United States. Much of this disease can be attributed to exposure to cigarette smoke. In fact, the surgeon general has listed cigarette smoking as one of the top three risk factors for the development of coronary heart disease.

The long-term objective of our work is to derive an understanding of the events that lead to the progression of mature atherosclerotic plaques. Current theory of how atherosclerotic plaques develop is shaped by the response to injury hypothesis. The essence of this hypothesis is that the pathological progression to mature atherosclerotic lesions results from an initial injury to the endothelium. In the case of smokers, this injury may result from exposure of the endothelium to tobacco derivatives. The injured endothelial cells respond by expressing adhesion molecules on their surface which promote the adhesion of circulating monocytes to the site of the injury. This patch of adherent monocytes is thought to be the earliest detectable atherosclerotic lesion, the fatty streak.

We intend to investigate the protein biochemistry of integrin $\alpha_4\beta_1$, a cell adhesion receptor on the surface of monocytes that mediates the adhesion of monocytes to cytokine activated endothelial cells. Integrin $\alpha_4\beta_1$ has two ligands, fibronectin and vascular cell adhesion molecule-1 (VCAM). VCAM is expressed only on the surface of cytokine activated endothelial cells, and has been localized to the endothelial cell surface in early atherosclerotic lesions. We hypothesize that VCAM and fibronectin potentiate the binding of each other to integrin $\alpha_4\beta_1$, leading to a complex between the three molecules. This complex would result in the tight adhesion of monocytes to the endothelial cell surface. Moreover, the immobilization of fibronectin, which contains six cell adhesion sequences, at the early lesion, would provide a potent adhesive surface for the recruitment of additional monocytes, macrophages and platelets to the atherosclerotic plaque.

To test this hypothesis we intend to define the protein-protein interactions between integrin $\alpha_4\beta_1$ and its ligands. The specific aims of this proposal are to: 1) define the relationship between fibronectin and VCAM binding to integrin $\alpha_4\beta_1$ by performing a quantitative analysis of the binding of the two ligands and this integrin in a purified system and on the cell surface; 2) identify the fibronectin binding site within integrin $\alpha_4\beta_1$ by photoaffinity labeling the receptor with small synthetic peptides derived from an adhesive sequence within fibronectin; 3) identify the $\alpha_4\beta_1$ recognition sequence within VCAM with a series of standard biochemical and immunological approaches. It is anticipated that completion of these aims will further the current knowledge of atherogenesis and may provide the rationale for the design of therapeutics to inhibit this process.

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Principal Investigator: Robert I. Macey

ABSTRACT

Interaction of Cadmium with Sickle Red Cells

Title of Research Project (do not exceed 60 spaces)

Molecular and Cell Biology, Regents of University of California, Berkeley

Department and Institution

We propose to test the hypothesis that sickle cells are particularly vulnerable to cadmium ingested in tobacco smoke. We suggest that in sickle cell disease low doses of cadmium pose significant challenges because Cd will enter the cell during deoxygenation. Because of its extremely high affinity for the Ca pump, it will inhibit Ca extrusion at very low Cd concentrations. The resultant increase in internal Ca will result in K leakage together with cellular dehydration, HbS polymerization, increased sickle and dense cell formation, and loss of cell deformability; these phenomena are important because they lead to an increased probability of vascular occlusion and sickle cell crisis. To test this hypothesis and to assess the potential hazards of Cd toxicity for this population (SS disease) we will apply a number of techniques developed in our laboratory to answer the following: Does cadmium treatment cause excessive polymer formation in SS cells? Is dehydration of SS red cells particularly susceptible to cadmium? Does cadmium treatment accelerate dense cell production in SS cells? Does cadmium treatment accelerate potassium loss in SS cells? Does cadmium treatment increase calcium accumulation in SS cells? Is the loss of deformability in SS red cells particularly susceptible to cadmium? Does cadmium treatment cause surface charge changes in SS cells? Does cadmium treatment cause internal viscosity changes in SS cells? Are SS reticulocytes particularly sensitive to cadmium? How does cadmium treatment influence the O2 dissociation curve in SS cells? How do oxidized cells respond to the above? How are all of these effects modulated by metallothionein buffering of Cd? How do levels of plasma and red cell Cd compare in smokers and non-smokers with sickle cell anemia?

2023470978

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Ruoslahti, Erkki

ABSTRACT

THE ROLE OF TGF-β1 IN INTIMAL HYPERPLASIA

Title of Research Project (do not exceed 60 spaces)

Cancer Research Center, La Jolla Cancer Research Foundation

Department and Institution

Smoking is a major risk factor for atherosclerotic vascular obstructions which often require balloon angioplasty or surgical reconstruction. Intimal hyperplasia (IH), which results in restenosis, is the major impediment to long term patency following these procedures. Most studies have focused on early migration and proliferation of vascular smooth muscle cells (SMC) after arterial injury. However, persistence of the process, rather than the initial proliferative surge, results in progressive accumulation of extracellular matrix (ECM) which acccunts for 80% of the volume in the obstructive lesion. Information from correlative studies implicates transforming growth factor-β1 (TGF-β1) as a central factor in IH. TGF-β1 transcript levels are elevated in the arterial wall early after injury and remain elevated for at least 2 weeks and administration of TGF-β1 after arterial injury results in increased SMC proliferation. TGF-β1 enhances production of ECM by SMC in vitro and is increased in several diseases associated with pathological accumulation of ECM, including mesangioproliferative glomerulonephritis (GN). Our laboratory has recently reported on down-regulation of TGF-β1 by the proteoglycan decorin, and treatment of experimental GN with this substance has proven successful.

We propose that TGF-β1 is a crucial factor in the late phase of IH and that it functions by inducing ECM deposition. This process may be self-limiting as a result of inhibition of TGF-β1 activity by accumulating ECM proteoglycans. Early delivery of such a signal may arrest the process prior to the formation of an obstructive lesion.

The purpose of this IDEA project is to prove or disprove a causative role for TGF-β1 in IH and to identify the factor/s that initiate and maintain TGF-β1 elevation. Down-regulation of TGF-β1, which is expected to result in attenuation of IH, will be effected with decorin in the rat carotid injury model. In addition, the temporal pattern of TGF-β1 transcript levels in untreated injured arteries will be related to its expression, assessed by immunohistochemistry, and its activity. The presence of TGF-β1 inducing factor/s will be examined by application of conditioned media or homogenates of injured arteries to SMC in culture which will be assayed for TGF-β1 transcript levels and TGF-β1 activity. These results may provide significant new information on the pathogenesis of this important smoking related disease and may suggest a novel therapy.

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TOBACCO-RELATED DISEASE RESEARCH PROGRAM

Cardiovascular Disease Study Section

Roster

Chairman

Lawrence Horwitz, M.D.
University of Colorado
Health Sciences Center
Division of Cardiology B-130
4200 East 9th Avenue
Denver, CO 80262

Members

Andre Bensadoun, Ph.D.
Div. of Nutritional Sciences
321 Savage Hall
Cornell University
Ithaca, New York 14853

Thomas Colatsky, Ph.D.
Division of Cardiovascular
and Metabolic Disorders
Wyeth-Ayerst Research
CN 8000
Princeton, New Jersey 08543

Peter Davies, Ph.D.
Department of Pathology
The University of Chicago
5841 S. Maryland Ave., Box MC3083
Chicago, Illinois 60637-1470

Mark Gillespie, Ph.D.
Division of Pharmacology
& Experimental Therapeutics
University of Kentucky
Rose Street, Room 415
College of Pharmacy
Lexington, Kentucky 40536-0082

Allan Jaffe, M.D.
Washington University
School of Medicine
Cardiology
660 South Euclid
St. Louis, Missouri 63110

Howard L. Kantor, M.D., Ph.D.
Cardiac Unit
Bulfinch Basement, Room 031
Massachusetts General Hospital
Fruit Street
Boston, Massachusetts 02114

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Norman L. Lasser, M.D., Ph.D.
Preventive Cardiology Program
University of Medicine
and Dentistry of New Jersey
New Jersey Medical School
Martland Building, GB20
65 Bergen Street
Newark, New Jersey 07107

Ivan McMurtry, Ph.D.
University of Colorado
Health Sciences Center
CVP Research Lab B-133
4200 East 9th Avenue
Denver, Colorado 80262

Darwin Labarthe, M.D.
School of Public Health
University of Texas
Science Center at Houston
1200 Herman Pressler Street
Houston, Texas 77030 RAS-E-101

John Parks, Ph.D.
Dept. of Comparative Medicine
Bowman Gray School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1040

Benedict Lucchesi, M.D., Ph.D.
Department of Pharmacology
M7423 Medical Science Bldg. 1
University of Michigan
Medical School
1301 East Catherine
Ann Arbor, Michigan 48109-0626

Henry J. Pownall, Ph.D.
Division of Atherosclerosis
and Lipoprotein Research
Dept. of Internal Medicine
Baylor College of Medicine
6535 Fannin, M.S. A-601
Houston, Texas 77030

Richard Majack, Ph.D.
Department of Pediatrics
University of Colorado
Health Sciences Center
4200 East Ninth Ave., Box B133
Denver, Colorado 80262

Gerald Roth, M.D.
Hermatology Section
Seattle Veterans Administration
Medical Center (111)
1660 South Columbian Way
Seattle, Washington 98108

Mark Majesky, Ph.D.
Department of Pathology
Baylor College of Medicine
1 Baylor Plaza
Houston, Texas 77030

Howard Silverman, M.D.
Medicine and Cardiology
Halsted 500
Johns Hopkins Hospital
School of Medicine
600 North Wolfe Street
Baltimore, Maryland 21205

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Manfred Steiner, M.D.
Div. of Hematology/Oncology
Memorial Hosp. of Rhode Island
111 Brewster Street
Pawtucket, Rhode Island 02860

Gordon Tomaselli, M.D.
Div. of Cardiology, 844 Ross
Johns Hopkins Sch. of Medicine
720 North Rutland Avenue
Baltimore, Maryland 21205

Dorothy Vatner, M.D.
New England Regional
Primate Research Center
1 Pinehill Drive
Southborough, MA 01772-0266

Ad Hoc Member

Libby Blankenhorn, Ph.D.
Department of Microbiology
& Immunology, MS410
New College Bldg., Room 10320
Hahneman University
Broad and Vine Streets
Philadelphia, PA 19102

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Pulmonary Disease

2023470984

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0100

Pulmonary Disease
Funded Projects

Research Awards

Bokoch, Gary M.	Sites of Chemoattractant Receptor Interaction with G Protein	The Scripps Research Institute
Ernst, Joel D.	Role of Annexins in Neutrophil Degranulation	University of California, San Francisco
Ganz, Tomas	Defensins and α2-Macroglobulin in Lung Inflammation	University of California, Los Angeles
Roth, Michael D.	Regulation of Natural Killer Cell Activity by Theophylline	University of California, Los Angeles
Spragg, Roger G.	Smoking Related Abnormalities of the Lung Surfactant System	University of California, San Diego
Wu, Reen	Pathogenesis of Smoke-Induced Injury in Airway Epithelium	University of California, Davis

IDEA Awards

Catanzaro, Antonino	Smoker Macrophage Response to Mycobacteria	University of California, San Diego
Szoka, Francis C.	Gene Therapy for Emphysema	University of California, San Francisco

2023470985

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: BOKOCH, Gary M.

ABSTRACT

Sites of chemoattractant Receptor Interaction with G Proteins

Title of Research Project (do not exceed 60 spaces)

Department of Immunology, The Scripps Research Institute

Department and Institution

The contribution of increased influx and activity of neutrophils and macrophages to cigarette smoke-induced lung injury is well documented. The underlying mechanisms of neutrophil chemotactic factor-stimulated activation involve signal transduction events between such receptors(R) and pertussis toxin-sensitive GTP binding (G) protein(s). The rationale for our studies is that understanding the specific molecular interactions underlying R-G interactions and the cellular mechanisms for regulating such interactions will lead to development of agents able to specifically disrupt chemoattractant receptor activation of neutrophils, attenuating tobacco-associated lung injury.

The ability of the N-formyl peptide receptor (NFP-R) to couple to specific G protein α and β/γ subunits will be evaluated in phospholipid vesicle and soluble reconstitution systems. Sites involved in the interactions of the two molecules will be probed using sequence-specific peptides and peptide antibodies, as well as NFP-R -derived fusion proteins. Site-directed mutagenesis of NFP-R and G protein will be pursued to verify results obtained with the former probes. Finally, we will utilize specific ELISA to identify low molecular weight compounds able to disrupt the interactions of NFP-R and G, then study the structural features of these inhibitors and their mechanisms of action using the reconstitution methodologies developed as part of these studies.

2023470986

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: ERNST, JD

ABSTRACT

ROLE OF ANNEXINS IN NEUTROPHIL DEGRANULATION

Title of Research Project (do not exceed 60 spaces)

MEDICINE/SFGH/UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Department and Institution

The link between cigarette smoke and chronic obstructive pulmonary disease, including emphysema, is established beyond any reasonable doubt. Smoking contributes both to inactivation of protective protease inhibitors, and causes accumulation of neutrophils in the lungs. Neutrophils, or polymorphonuclear leukocytes (PMN), are the sole source of neutrophil elastase, an enzyme strongly implicated in causing the irreversible damage to pulmonary alveolar septa characteristic of emphysema. In order for elastase to digest elastin and other extracellular matrix proteins in the lung, it must be secreted from PMN, where it is normally sequestered in membrane-bound azurophil granules. Central to elastase secretion is the phenomenon of degranulation, whereby the contents of PMN granules are discharged to the extracellular space, via fusion of granule membranes with portions of the plasma membrane. The objective of the proposed research is to further our understanding of the molecular basis of PMN degranulation. We will test the hypothesis that members of the annexin family of Ca^{2+}- and membrane-binding proteins are essential components of a regulated, specialized system that mediates membrane fusion and degranulation in human PMN. We have purified, identified, and characterized seven distinct members of the annexin protein family, and found that the individual proteins have distinct functional properties, including the ability to promote membrane-membrane contact at Ca^{2+} concentrations similar to those in stimulated PMN. In addition, we discovered that when PMN ingest opsonized yeast, at least two of these proteins are found concentrated in the region of the cell immediately surrounding the phagocytic vesicle. Moreover, we developed a new method for permeabilizing the plasma membrane of PMN that causes depletion of their cytoplasmic proteins. Using this new method, we found that annexin I reconstitutes degranulation of permeabilized PMN stimulated with Ca^{2+}. We will extend these studies and further characterize the annexins that regulate PMN degranulation. We will test the hypotheses that other second messengers regulate the activities of annexins, and that annexins interact with other intracellular proteins in a regulated system that mediates membrane fusion in degranulation. In addition, we will test the hypothesis that annexins localize to specific membrane sites in stimulated PMN. The studies outlined in this proposal should yield significant new information regarding the mechanism of degranulation of PMN, and may lead to novel approaches to the control of this process in diverse disease states including pulmonary emphysema.

2023470987

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Ganz, Tomas, Ph.D., M.D.

ABSTRACT

Defensins and α2-macroglobulin in lung inflammation

Title of Research Project (do not exceed 60 spaces)

Department of Medicine, University of California, Los Angeles

Department and Institution

Chronic bronchitis and emphysema are the consequences of inflammation induced by the inhalation of tobacco smoke. Although tobacco-induced injury to the airways is detectable in all smokers, for unknown reasons only a minority develop progressive destructive changes that lead to disability and death. The partial success of the "protease-antiprotease balance" paradigm has led to the more general hypothesis that individual susceptibility to tobacco-induced pulmonary injury is a result of imbalance between proinflammatory and antiinflammatory mechanisms. We propose that α2-macroglobulin functions as an important antiinflammatory factor in the lung, in part by scavenging proteases and other proinflammatory peptides, and delivering them to macrophages for degradation. Our data suggest that an important and previously unknown function of α2-macroglobulin may be its ability to bind defensins, major proinflammatory peptides of human neutrophils.

We propose to elucidate the molecular determinants of interaction between α2-macroglobulin and defensins and define the relevant binding sites. We will measure the ability of α2-macroglobulin to facilitate the uptake of defensins by alveolar macrophages, and determine the subsequent intracellular metabolism of defensins. We will analyze how defensin binding by α2-macroglobulin is modulated by reactive oxygen intermediates produced by neutrophils, and by cadmium, a toxic ingredient of tobacco smoke with high affinity for α2-macroglobulin. We will study the ability of α2-macroglobulin to inhibit such defensin activities as cytotoxicity and monocyte chemoattraction, and examine the competition between defensins and other cationic or proinflammatory peptides for binding sites on α2-macroglobulin.

We will then examine and compare bronchoalveolar lavage fluids (BALF) from smokers and non-smokers, with respect to concentration of defensins and the two major forms of α2-macroglobulin. We will assay the BALF for the presence of other defensin-binding proteins.

Through this study of basic mechanisms of inflammation, we are likely to gain new insights into the the pathogenesis of tobacco-induced lung disease. In the longer term, the findings of this study may impact on the identification of persons at risk for disabling tobacco-induced lung disease and lead to novel preventive and therapeutic approaches.

2023470988

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Michael D. Roth, M.D.

ABSTRACT

REGULATION OF NATURAL KILLER CELL ACTIVITY BY THEOPHYLLINE

Title of Research Project (do not exceed 60 spaces)

DEPARTMENT OF MEDICINE, UCLA SCHOOL OF MEDICINE

Department and Institution

Theophylline is commonly prescribed for the treatment of tobacco-induced COPD. In addition to its well known side effects on the heart, brain, and kidneys, theophylline also interferes with the function of T-cells and natural killer (NK) cells. Increasing evidence suggests that these immune effectors play an important role in the host's response to tumor growth. The combination of chronic immunosuppression by theophylline, and the increased cancer risk associated with COPD, may adversely impact on the health of this group of tobacco smokers. This proposal will examine the capacity for, and the mechanisms by which, therapeutic levels of theophylline inhibit the tumoricidal activity of NK cells. We will examine whether theophylline disrupts the capacity for NK cells to recognize and bind tumor, or whether it alters the kinetics of NK-mediated tumor lysis. Theophylline can alter cell function by at least two pathways; inhibition of intracellular phosphodiesterase (PDE) and antagonism of cell surface adenosine receptors. Utilizing the opposing characteristics of theophylline, which is a weak PDE inhibitor but a potent adenosine antagonist, and enprofylline, which is a potent PDE inhibitor but a weak adenosine antagonist, we will determine which pathway mediates NK suppression. In preliminary work, therapeutic levels of enprofylline did not inhibit tumor lysis by NK cells. To confirm the differential effects of adenosine antagonism and PDE inhibition on NK cell function, we will study changes in NK cell function mediated by 8-phenyltheophylline (8-PT), a relatively pure adenosine antagonist and by papaverine, a PDE inhibitor without adenosine receptor activity. In addition, we will correlate the effects of all four drugs to their capacity to alter the second messenger signal pathways important in NK-mediated tumor lysis (Ca^{++} mobilization and [cAMP]). This will provide an important link between the pharmacologic effects of theophylline and the intracellular pathways which regulate NK responsiveness. Finally, we will translate our results into a clinical study to confirm that therapeutic levels of theophylline suppress NK activity in-vivo. Our goal is to better understand the regulation of anti-cancer immunity in the population of smokers which is at the highest risk for lung cancer. This study will establish the basic immunosuppressive potential of theophylline as well as define the pharmacologic and second messenger pathways which mediate its effects.

2023470989

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Roger G. Spragg

ABSTRACT

SMOKING RELATED ABNORMALITIES OF THE LUNG SURFACTANT SYSTEM

Title of Research Project (do not exceed 60 spaces)

Department of Medicine, University of California, San Diego

Department and Institution

Prior studies have demonstrated reduced function and concentration of lung surfactant (LS) in fluids recovered from the lungs of chronic smokers. This application proposes investigations focused on understanding the causes of abnormalities of the LS system in smokers.

A variety of powerful oxidants, including H_2O_2 and $O_2^{\cdot}$, are generated in both the vapor phase and particulate phase of cigarette smoke. These oxidants are delivered directly to the alveolar epithelium of the lung that is lined by lung surfactant. In addition, smokers have increased numbers and activity of inflammatory cells in the lower airway. These cells generate both oxidants and proteases. We postulate that oxidants in cigarette smoke and oxidants and proteases from inflammatory cells result in chemical alteration and functional impairment of the surfactant system of the lung. This premise rests on preliminary data from experiments in which we exposed lung surfactant to chemical oxidizing systems or tobacco smoke and found evidence of formation of products of lipid peroxidation and/or loss of surface tension lowering activity. In addition, prior work of others suggests that surfactant apoproteins are targets of several proteases released from inflammatory cells.

We will examine two general hypotheses: (1) oxidation of LS in the inflamed lung of smokers results in surfactant oxidation and loss of surfactant surface activity; and (2) exposure of LS to proteases in the inflamed lung of smokers results in surfactant apoprotein cleavage with associated loss of surface activity. To address these hypotheses, we will: (a) detect the presence of LS-specific oxidation products in bronchoalveolar lavage fluid (BAL) from smokers; (b) determine if products of activated neutrophils are capable of causing loss of LS function *in vitro*; (c) define the consequences of LS oxidation that are responsible for loss of surface activity; and (d) search for evidence of LS apoprotein cleavage in samples of BAL from smokers using reagents developed during this investigation.

Discovery of significant loss of LS surface activity will suggest that an important component of inflammatory lung injury is alteration of the biophysical properties of the alveolar surface film. This alteration may result in increased alveolar wall tension and contribute to the development of pulmonary emphysema. Our results will enhance understanding of tobacco-related lung diseases, stimulate further research into the causes of pulmonary emphysema, and suggest therapeutic strategies.

2023470990

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Reen Wu

ABSTRACT

Pathogenesis of Smoke-Induced Injury in Airway Epithelium

Title of Research Project (do not exceed 60 spaces)

California Primate Research Center, University of California, Davis

Department and Institution

The University of California at Davis recently acquired a state-of-the-art facility that allows us to expose small laboratory animals or cultured cells to known concentrations of chemically well-characterized environmental tobacco smoke (ETS). Only minor modifications will be needed to conduct exposure studies with mainstream tobacco smoke (MTS). The exposure facility was installed and monitored by scientists from the Analytical Chemistry Division of Oak Ridge National Laboratory, a group preeminent for their experience in tobacco smoke generation and analysis. In the PI's laboratory, a biphasic cell culture system was developed to grow and to maintain differentiated airway epithelium between the air phase and the liquid medium. This system is suitable for in vitro tobacco smoke exposure studies.

Cigarette smoking is associated with an increased risk for developing chronic bronchitis, emphysema, and lung cancer. A common feature of these diverse lung diseases is the abnormal proliferation of bronchial epithelium. The nature of this phenomenon is not known. We hypothesize that the alterations in cell proliferation may involve "autocrine and/or paracrine" regulation by growth factor(s) secreted in smoke-exposed epithelium. A preliminary study supports this hypothesis and suggests that activity like that of transforming growth factor-alpha (TGF-α) is involved in the growth regulation. To further elucidate this mechanism, we will 1) quantify dose-response relationships between concentrations of ETS or MTS, the resultant cell damage, and TGF-α gene expression; 2) elucidate the nature of the regulation of TGF-α expression by cigarette smoke in primary human and monkey tracheobronchial epithelial cultures; and 3) determine the autocrine and/or paracrine nature of the smoke-induced TGF-α in the regulation of cell growth and differentiation.

A cDNA probe and antibodies specific to TGF-α and an epidermal growth factor (EGF) receptor have been obtained. A RNA-PCR method has been developed to quantify the TGF-α message level. Nuclear run-on and inhibitor studies will be used to determine whether the regulation occurs at the transcriptional or post-transcriptional levels. In situ hybridization and immunohistochemistry will be used to identify cell type-specific gene expression. Anti-sense RNA strategies and immunological inhibition of TGF-α activity will be used to determine the nature of autocrine and/or paracrine regulation. These studies, in conjunction with a time course study, a dose-response study, and a morphological analysis will establish the role of TGF-α in tobacco smoke-induced lung diseases.

2023470991

DOOR

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Antonino Catanzaro, M.D.

ABSTRACT

SMOKER MACROPHAGE RESPONSE TO MYCOBACTERIA

Title of Research Project (do not exceed 60 spaces)

Department of Medicine, University of California, San Diego

Department and Institution

Smokers suffer an increase in respiratory infections and alteration in the inflammatory responses. The alveolar macrophage is one of the major components of the host response to respiratory infections and an integral part of the local inflammatory response in the lungs. The major functions of macrophages are attachment of microbes and cytokine production. An improved understanding of these aspects of macrophage function may help in the understanding of the pathology seen in smokers. *Mycobacterium avium-intracellulare* complex (MAC) is a group of organisms that is commonly found in the environment. Infection due to MAC is uncommon in non-immunocompromised people. However, smokers, particularly those with chronic obstructive pulmonary disease (COPD), can have serious pulmonary infection due to MAC. In non-immunocompromised patients with MAC infection, 30-60% have COPD due to smoking. What the local factors are that are responsible for this observation is unknown. However, macrophages are the host cell primarily responsible for phagocytosis and killing of MAC. The receptors on macrophages utilized for attachment by MAC may influence the fate of MAC and thereby the course of infection. This laboratory has purified and identified a receptor on monocytes/macrophages which binds MAC in the absence of opsonins, is trypsin sensitive, independent of cations and mobile in the plane of the membrane. The receptor has been identified as the vitronectin receptor (VnR). These data demonstrate that VnR is a receptor on monocytes which binds MAC. Furthermore, a 65 kD ligand has been isolated from MAC which blocks binding of MAC to MDM. The receptor and ligand characterized in this laboratory will be used to 1) determine the ability of host cells from non-smokers and smokers to express VnR on their surface and to bind MAC; 2) characterize binding of the 65 Kd MAC ligand to cells from non-smokers and smokers 3) study the role of MAC-derived VnR-binding ligands and VnR in the binding and phagocytosis of MAC, and 4) expose macrophages from smokers and non-smokers to MAC and characterize the response in terms of mRNA for important cytokines such as GMCSF, TNF, IL-1, and the IL-1 receptor antagonist.

An understanding of the macrophage response to mycobacteria may offer new insights into the adverse effects of smoking on macrophages as well as to the pathogenesis of the pulmonary problems of smokers.

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Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Francis C. Szoka, Jr. Ph.D.

ABSTRACT

Gene Therapy for Emphysema

Title of Research Project (do not exceed 60 spaces)

Pharmaceutical Chemistry and Pharmacy, University of California, San Francisco

Department and Institution

The purpose of this research is to develop and test non-viral gene delivery systems for the treatment of emphysema in α-1-antitrypsin (AT) deficient patients. Treatment with a recombinant derived protein has been shown to replace the deficiency in this patient population. Viral gene delivery systems for AT replacement in the lung are under development but viral systems may create their own set of health problems, hence non-viral approaches should also be developed.

We will test the hypothesis that two non-viral gene delivery systems can efficiently transfect epithelial cells by direct administration of the delivery system into the lung. By improving nucleic acid delivery to lung tissue the AT protein can be produced in sufficient quantity to combat alveolar destruction and reverse or prevent disease. Non-viral mediated DNA treatment will minimize safety issues concerning viral infection in the patient.

The human AT gene has been cloned in entirety and is available in a mammalian expression plasmid from the American Type Culture Collection. The plasmid construct will be delivered *in vitro* and *in vivo* via pH-sensitive liposomes and ligand-acridine conjugates. pH-sensitive liposomes have been used extensively by our laboratory and have shown the ability to easily encapsulate and effectively deliver DNA to a variety of mammalian cell lines. The ligand-acridine conjugates allow the construction of the delivery system directly on the DNA. Lung surfactant protein-A (SP-A) will serve as ligand to direct plasmid to lung epithelial cells and a nuclear localization sequence (NLS) will be incorporated into the delivery complex to facilitate nuclear entry once DNA enters the cytoplasm. Both systems will initially be introduced to human epithelial cells in culture with a plasmid encoding ß-galactosidase. This reporter gene will allow easy visual detection of transfection and rapid optimization of the systems. The cationic liposome Lipofectin, will serve as the control system. The human AT gene will be delivered to Sprague Dawley rats intratracheally using both delivery systems. Control animals will be treated with plasmid and empty delivery systems. At various times after administration, the animals will be sacrificed and lung levels as well as lung lavage fluid levels of human AT protein will be detected by ELISA. Message levels will be quantitated by slot-blot analysis using ^{32}P labeled probes of cloned sequences from the human AT gene.

The ability to safely and effectively deliver the human AT gene in this animal model may lead to future gene therapy strategies for smokers with AT deficiency who suffer from emphysema.

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TOBACCO-RELATED DISEASE RESEARCH PROGRAM

Pulmonary Disease Study Section

Roster

Chairman

Attilio D. Renzetti, Jr., M.D.
University of Utah
Department of Medicine - Emeritus
School of Medicine
50 North Medical Drive
Salt Lake City, Utah 84132

Members

Kenneth B. Adler, Ph.D.
College of Veterinary Medicine
North Carolina State University
4700 Hillsborough Street
Raleigh, North Carolina 27606

James Gadek, M.D
The Ohio State University Hosp.
N325 Means Hall
1654 Upham Drive
Columbus, Ohio 43210

Joel Karlinsky, M.D.
Pulmonary Division
Room A-1182
Boston VA Medical Center
150 South Huntington Avenue
Boston, Massachusetts 02130

Jason Kelley, M.D.
University of Vermont
College of Medicine
Pulmonary Unit
Given Building, Given C-317
Burlington, VT 05405-0068

Mel Lopata, M.D.
Department of Medicine
840 South Wood Street M/C 787
Univ. of Illinois at Chicago
Chicago, Illinois 60612

Sadis Matalon, Ph.D.
Department of Anesthesiology
Univ. of Alabama at Birmingham
619 South - 19th Street-JT845
Birmingham, Alabama 35233-6810

John R. Michael, M.D.
Pulmonary Division
Room 4-R240
University of Utah Medical Center
50 N. Medical Drive
Salt Lake City, Utah 84132

Elizabeth Ann Perkett, M.D.
Vanderbilt University School of Medicine
Department of Pediatrics
Division of Pulmonary Medicine
S-0119 Medical Center North
1161 21st Avenue South
Nashville, Tennessee 37232-2586

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Lewis J. Rubin, M.D.
Division of Pulmonary
and Critical Care Medicine
University of Maryland
School of Medicine
10 South Pine Street, MSTF 800
Baltimore, Maryland 21201-1192

John Spurzem, M.D., M.S.P.H.
Pulmonary & Critical Care Med.
University of Nebraska
Medical Center
600 South 42nd Street
Omaha, Nebraska 68198-2465

Galen Toews, M.D.
Division of Pulmonary
& Critical Care Medicine
University of Michigan Hospital
1500 East Medical Center Drive
3916 Taubman
Ann Arbor, MI 48109-0360

Ad Hoc Member

David J. Riley, M.D.
Professor
Department of Medicine
UMDNJ
Robert Wood Johnson Med. School
Room C-B04
675 Hoes Lane
Piscataway, New Jersey 08854-5635

Sami I. Said, M.D.
SUNY at Stony Brook
Health Sciences Center
T17 040
Stony Brook, NY 11794-8172

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CARDIOVAS. & PULMONARY
DISEASE CAREER DEVELOP.

2023470996

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Cardiovascular and Pulmonary Disease Career Development

2023470997

Source: https://www.industrydocuments.ucsf.edu/docs/jvl0000

Cardiovascular and Pulmonary Disease Career Development
Funded Projects

New Investigator Awards

Cheek, Jeffrey M.	Environmental Tobacco Smoke & Epithelial Barrier Function	University of California, Davis
Gibbons, Gary H.	Mechanisms of Atherogenesis:Role of Shear Stress & Tobacco	Stanford University
He, Ping N.	Endothelial Barrier Injury by Tobacco Smoke	University of California, Davis
Villarreal, Francisco J.	Angiotensin II Regulation of the Cardiac Fibroblast	University of California, San Diego
Wong, Vicky L.	Nicotine and Hemostatic Function of Brain Endothelium	University of Southern California

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Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Cheek, Jeffrey M. [redacted]

ABSTRACT

Environmental Tobacco Smoke and Epithelial Barrier Function

Title of Research Project (do not exceed 60 spaces)

Department of Veterinary Medicine: Anatomy, University of California at Davis

Department and Institution

The study detailed in this proposal addresses several priority issues germane to relating pulmonary health effects and exposure to tobacco smoke. Continued progress in quantitatively assessing the relative risks of acute tobacco smoke injury requires the development of approaches that are capable of not only signalling that a biologically measurable exposure has occurred, but that the exposure has exceeded the ability of the tissue or cell to repair the injury. The central goal of the proposed work is to use simple model systems (lung epithelial cell cultures) to facilitate studies of relevant dosimetry and biological mechanisms by which tobacco smoke produces epithelial cell injury in the lung. Specifically, we plan to quantitatively define the role of free radical-mediated damage, produced by exposure to environmental tobacco smoke (ETS), in the acute impairment of epithelial barrier properties *in vitro*. Our working hypothesis is that the levels of free-radical generating species present in ETS are sufficient to induce cell injury and impair the integrity and function of the pulmonary epithelial barrier, rendering the lung more susceptible to subacute and chronic disease states. Primary cultures of epithelial cells isolated from conducting airways and alveolar tissues will be used as models of free radical-mediated injury resulting from exposure to ETS *in vitro*. Changes in tissue electrophysiologic properties will provide the primary quantitative assessment of ETS effects on epithelial barrier function. The biochemical basis for the sensitivities of airway and alveolar epithelial monolayers to oxidative stress will be evaluated by assays of antioxidant enzyme activities, glutathione levels, and antioxidant nutrient status (levels of Vitamins C and E). Alterations in barrier permeability will be compared to shifts in cytoskeletal structure, intracellular calcium concentration and paracellular junctional complexes. The relationship between exposure to ETS-generated free radicals and epithelial cell injury will be characterized using histochemical approaches to identify reactive secondary oxygen species and their distribution relative to ultrastructural pathology. Methodologies for assessing the degree of ETS injury in these *in vitro* models will be evaluated for their potential in future *in vivo* applications to facilitate the defining of ETS exposure levels pertinent to health effects. These multiple strategies should improve our understanding of the nature of ETS toxicity and enable us to test protocols for alleviating acute free radical-mediated injury.

2023470999

DOOR

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Gary H. Gibbons, M.D.

ABSTRACT

Mechanisms of Atherogenesis: Role of Shear Stress and Tobacco

Title of Research Project (do not exceed 60 spaces)

Division of Cardiovascular Medicine, Dept. of Medicine, Stanford University

Department and Institution

Atherosclerosis, a leading cause of tobacco-related mortality, is characterized by the abnormal proliferation of vascular smooth muscle cells (VSMC). Although the mechanisms of atherogenesis remain to be elucidated, a growing body of evidence suggests that hemodynamic stimuli play an important role in the development of these lesions at discrete loci within the vascular tree. Experimental studies have documented that the proliferation of VSMC after vascular injury is inhibited under conditions of increased flow or shear stress (the tractive force exerted by flow). These findings indicate that increases in flow may promote the local production of factors that prevent atherogenesis at certain loci. The endothelium is ideally situated to regulate this interaction between hemodynamic stimuli and VSMC growth regulation by sensing changes in flow and producing growth modulatory mediators. We postulate that tobacco smoke potentiates atherogenesis by impairing the capacity of the endothelium to produce growth inhibitory factors in response to shear stress. The objectives of the proposed project are: 1) to define the molecular mechanisms by which increased shear stress inhibits myoproliferation; and 2) to assess the effect of tobacco constituents on the capacity of the endothelium to modulate VSMC growth in response to shear stress.

Based on previous work in our laboratory, we postulated that transforming growth factor beta 1 (TGFβ1) may mediate the inhibitory effect of increased shear stress on VSMC growth. Indeed, in preliminary studies, we have demonstrated that exposure of cultured endothelial cells to shear stress *in vitro* induces increased mRNA levels of TGFβ1 and production of the active form of the peptide. The molecular mechanisms by which increased flow induces increased expression of active TGFβ1 remain to be clarified. Previous studies in our laboratory and others suggest that increased flow stimulates a cascade of cellular events involving a flow-sensitive potassium channel and activation of protein kinase C. We postulate that the activation of this signal transduction pathway by shear stress induces the co-expression of both TGFβ1 and tissue plasminogen activator (tPA). Given that TGFβ1 is normally secreted in an inactive latent form, we postulate further that the co-induction of tPA expression and the consequent generation of plasmin is necessary to proteolytically convert latent TGFβ1 to its biologically active form. Moreover, we hypothesize that inactivation of this signal transduction pathway by factors such as tobacco smoke will impair the capacity of the endothelium to inhibit myoproliferation in response to shear stress.

The proposed project will test these hypotheses by characterizing the signal transduction pathway mediating the coordinated induction of TGFβ1 and tPA mRNA expression by shear stress. Furthermore, we will define the roles of plasminogen activator and active TGFβ1 as mediators of the inhibitory effect of increased flow on myoproliferation. In addition, we will test the hypothesis that constituents of tobacco smoke potentiate myoproliferation by impairing the capacity of the endothelium to produce active TGFβ1 in response to shear stress. The results of the proposed studies will provide new insights into the molecular mechanisms governing the interaction between hemodynamic stimuli, tobacco smoke and vascular cell growth regulation. We anticipate that investigation of the molecular mechanisms by which hemodynamic stimuli and tobacco smoke modulate VSMC growth will foster the discovery of novel preventive strategies in the treatment of vascular disease.

2023421000

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: HE, Ping N.

ABSTRACT

Endothelial Barrier Injury by Tobacco Smoke

Title of Research Project (do not exceed 60 spaces)

Department of Human Physiology, University of California Davis

Department and Institution

The objective of my research is to investigate the calcium dependent mechanisms of injury to endothelial barriers. Previous findings from our laboratory, and by other investigators, indicate that the products of tobacco smoke extract increase the permeability of cultured endothelial cell monolayers and intact microvessels by calcium dependent processes. The specific aims of the proposed research are to test three hypotheses:

1). Increased calcium ion influx into endothelial cells is one of the mechanisms to elicit an increase in permeability induced by mediators of inflammation and free radicals generated by the cigarette smoke components.

2). The membrane potential of the endothelial cell is an important regulator of calcium ion influx.

3). The physical and chemical environment of the microvessel modifies the change in permeability and calcium influx associated with response to cigarette smoke and inflammatory stimulus.

I have developed methods to measure changes in cytoplasmic calcium concentration, $[Ca^{++}]_i$, and the membrane potential of endothelial cells forming the wall of individually perfused microvessels. I have found that in microvessels exposed to calcium ionophores, processes which tend to depolarize the membrane reduce calcium entry and microvessel permeability while processes which hyperpolarize the endothelial membrane increase calcium influx and permeability. Preliminary experiments suggest similar mechanism may regulate other high permeability states, such as those induced by free radicals which are rich in cigarette smoke, or by some inflammatory mediators. To test these hypotheses I will use microperfusion methods to measure $[Ca^{++}]_i$, calcium influx, and the changes in permeability will be measured as changes in hydraulic conductivity, Lp, under identical experimental conditions. Permeability will be increased using receptor dependent and receptor independent changes in permeability in venular microvessel of frog and hamster mesentery. Hypoxanthine and xanthine oxidase will be used to generate the free radicals to mimic the effect of cigarette smoke components. I will use ion substitution experiments to modify calcium influx into the endothelial cells, and measure the corresponding change in cytoplasmic free calcium concentration as permeability is increased and decreased. In this way the calcium dependent mechanisms which modulate microvessel permeability can be studied under the same experimental conditions as those where permeabilities are measured. These methods provide me with the means to investigate the interactions of endothelial barriers with the components of tobacco smoke and the general mechanisms related to the endothelial barrier injury induced by a variety of agents. These methods also provide a bridge between investigations of the cellular processes which regulate permeability in cultured endothelial cell monolayers and investigations of the modulation of permeability in intact microvessels.

2023471001

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Francisco J. Villarreal

ABSTRACT

ANGIOTENSIN II REGULATION OF THE CARDIAC FIBROBLAST

Title of Research Project (do not exceed 60 spaces)

Department of Medicine University of California, San Diego

Department and Institution

One of the most important medical consequences of cigarette smoking is the increased incidence of cardiovascular diseases such as angina pectoris and myocardial infarction (coronary heart disease). In addition, smoking aggravates the clinical course of hypertensive patients and increases the activity of the plasma renin-angiotensin-aldosterone system. Secondary cardiac hypertrophy is a pathological entity that frequently develops as a result of myocardial infarction and hypertension. The development of pathological hypertrophy in the myocardium has been associated with an abnormal accumulation of extracellular matrix proteins (mostly collagens) in the interstitium. Cardiac fibroblasts constitute up to two thirds of the myocardial cell population and are responsible for the production of the extracellular matrix (ECM) proteins fibronectin and collagens types I and III. Although it has been demonstrated that fibroblasts have the capacity to express angiotensin II (Ang II) receptors, nothing is known about the ability of Ang II to regulate function in fibroblasts of cardiac origin. However, recent evidence has been accumulating in the literature regarding the potential trophic role of Ang II in the development of myocardial fibrosis. Moreover, a local renin-angiotensin system has been identified to operate in the myocardium. The overall objective and long term goal of this proposal is to determine the potential role that Ang II plays in regulating cardiac fibroblast function. We propose to determine if cardiac fibroblasts express receptors for Ang II and to examine if the receptor density and subtype varies with the developmental stage of the animal and/or the presence of cardiac hypertrophy. We will also examine the ability of Ang II to regulate the gene expression of ECM proteins fibronectin and collagen types I and III by assesing changes in mRNA and protein levels. Results will be contrasted to those obtained from fibroblasts isolated from adult rat skin. To examine the nature of the molecular mechanisms responsible for the increase in ECM protein production, nuclear runoffs as well as mRNA stability assays will be performed. Finally, in order to determine if Ang II plays a role in regulating the deposition of ECM protein in an in-vivo environment, we will utilize a novel model that involves the selective disruption of the extracellular matrix after an initial insult with a disulfide chemical agent. Two groups of young adult rats will be exposed to this agent, selectively destroying extracellular matrix proteins by activating endogenous collagenases. One group of rats will be allowed to "heal" (i.e. control group) while the second group of rats will be treated with an angiotensin converting enzyme inhibitor such as enalapril. Physiological and biochemical assays will be used to determine if Ang II regulates the in-vivo deposition of ECM proteins.

2023471002

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Vicky Wong

ABSTRACT

Nicotine and Hemostatic Function of Brain Endothelium

Title of Research Project (do not exceed 60 spaces)

Department of Neurology, USC School of Medicine

Department and Institution

Stroke is the third leading cause of death in North America and smoking is a major stroke risk factor. The pathogenic mechanism(s) relating smoking to stroke is incompletely understood. However, there is evidence that smoking components, e.g., nicotine, are associated with altered endothelial function. Our study will focus on hemostatic function of capillary endothelial cells of the brain and their regulation by astrocytes and nicotine. Astrocytes will be studied, since they are often in close proximity to brain capillary endothelial cells and share a common basement membrane. We hypothesize that nicotine increases the risk for ischemic stroke by altering endothelial hemostatic function of the brain directly, or indirectly via potentiating astrocyte-endothelial interaction. We will test our hypothesis by exposing bovine brain capillary endothelial cells to astrocyte conditioned medium or nicotine to determine the effects on hemostatic proteins, e.g. thrombomodulin (the endothelial anticoagulant integral membrane protein) or tissue factor (the inducible procoagulant protein). Co-cultures of astrocytes and endothelial cells will also be treated with nicotine to determine if nicotine's effects on hemostasis require intimate astrocyte-endothelial interaction. Our preliminary data suggest that astrocytes secrete a soluble factor(s) that down-regulates thrombomodulin function and up-regulates tissue factor expression in endothelial cell culture; nicotine also appears to down-regulate thrombomodulin activity in brain capillary endothelial cells either alone or synergistically with astrocyte conditioned medium. Knowledge of how nicotine alters hemostatic function of brain endothelial cells will provide understanding of pathogenic mechanisms of smoking as a stroke risk factor.

2023421003

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TOBACCO-RELATED DISEASE RESEARCH PROGRAM

Cardiovascular and Pulmonary Career Development Study Section

Roster

Merle S. Olson, Ph.D.
The University of Texas
Health Science Center
Department of Biochemistry
7703 Floyd Curl Drive
San Antonio, Texas 78284-3719

Members

Susan C. Frost, Ph.D.
Department of Biochemistry
& Molecular Biology
University of Florida
College of Medicine
Box J-245, JHMHC
Gainesville, FL 32610

Charles Hiller, M.D.
University Hospital
Slot 555
4301 West Markham
Little Rock, Arkansas 72205

Carl A. Gruetter, Ph.D.
Department of Pharmacology
Marshall University
School of Medicine
1542 Spring Valley Drive
Huntington, WV 25755-9310

Ronald J. Korthuis, Ph.D.
Department of Physiology
Louisiana State University
Medical Center
1501 Kings Highway
Shreveport, Louisiana 71130

Dennis D. Hickstein, M.D.
Division of Hematology
Medical Service (111),
Building 1, Room 166
Seattle Veteran's
Administration Medical Center
1660 South Columbian Way
Seattle, Washington 98108

Diana M. Lee, Ph.D.
Lipoprotein/Atherosclerosis
Research Program
Oklahoma Med. Research Foundation
825 North East 13th Street
Oklahoma City, Oklahoma 73104

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James Martins, M.D.
College of Medicine
E318-3 General Hospital
University of Iowa
Iowa City, Iowa 52242

Jacob I. Sznajder, M.D.
Department of Medicine
Humana Michael Reese Hospital
University of Illinois at Chicago
Lake Shore Drive at 31st RC223
Chicago, Illinois 60616

Thomas M. McIntyre, Ph.D.
Department of Medicine
& Biochemistry
University of Utah
CVRTI, Building 500
Salt Lake City, Utah 84112

Thomas Tulenko, Ph.D.
Department of Physiology
& Biochemistry
Medical College of Pennsylvania
3300 Henry Avenue
Philadelphia, PA 19129

Michele Mercuri, M.D., Ph.D.
Division of Vascular
Ultrasound Research
Bowman Gray School of Medicine
300 South Hawthorne Road
Winston-Salem, N.C. 27103

Robert L. Van Citters, M.D.
University of Washington
School of Medicine
Department of Medicine
Cardiology, RG22
1959 N.E. Pacific St., Rm. E-303
Seattle, Washington 98195

David J. Riley, M.D.
Department of Medicine
UMDNJ-Robert Wood Johnson
Medical School
Room C-B04
675 Hoes Lane
Piscataway, NJ 08854-5635

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Ad Hoc Members

Raymond E. Idecker, M.D., Ph.D.
Duke University
403 Teer Engineering Building
Science Drive
Durham, NC 27706

Richard Schlesinger, Ph.D.
New York University Medical Center
Department of Environmental Medicine
Long Meadow Road
Tuxedo, NY 10987

Donald Primerano, Ph.D.
Marshall University
Department of Microbiology
School of Medicine
1542 Spring Valley Drive
Huntington, WV 25755-9330

Gordon Tomaselli, M.D.
Johns Hopkins School of Medicine
Division of Cardiology, 844 Ross
720 North Rutland Avenue
Baltimore, MD 21205

David H. Rutschman, Ph.D.
Northeastern Illinois University
Department of Mathematics
5500 North Saint Louis Avenue
Chicago, IL 60625-4699

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TOBACCO-RELATED DISEASE RESEARCH PROGRAM

July 1992

Grants Awarded in

Epidemiology and Behavior and Public Health Research on Tobacco

University of California
Office of Health Affairs

2023471008

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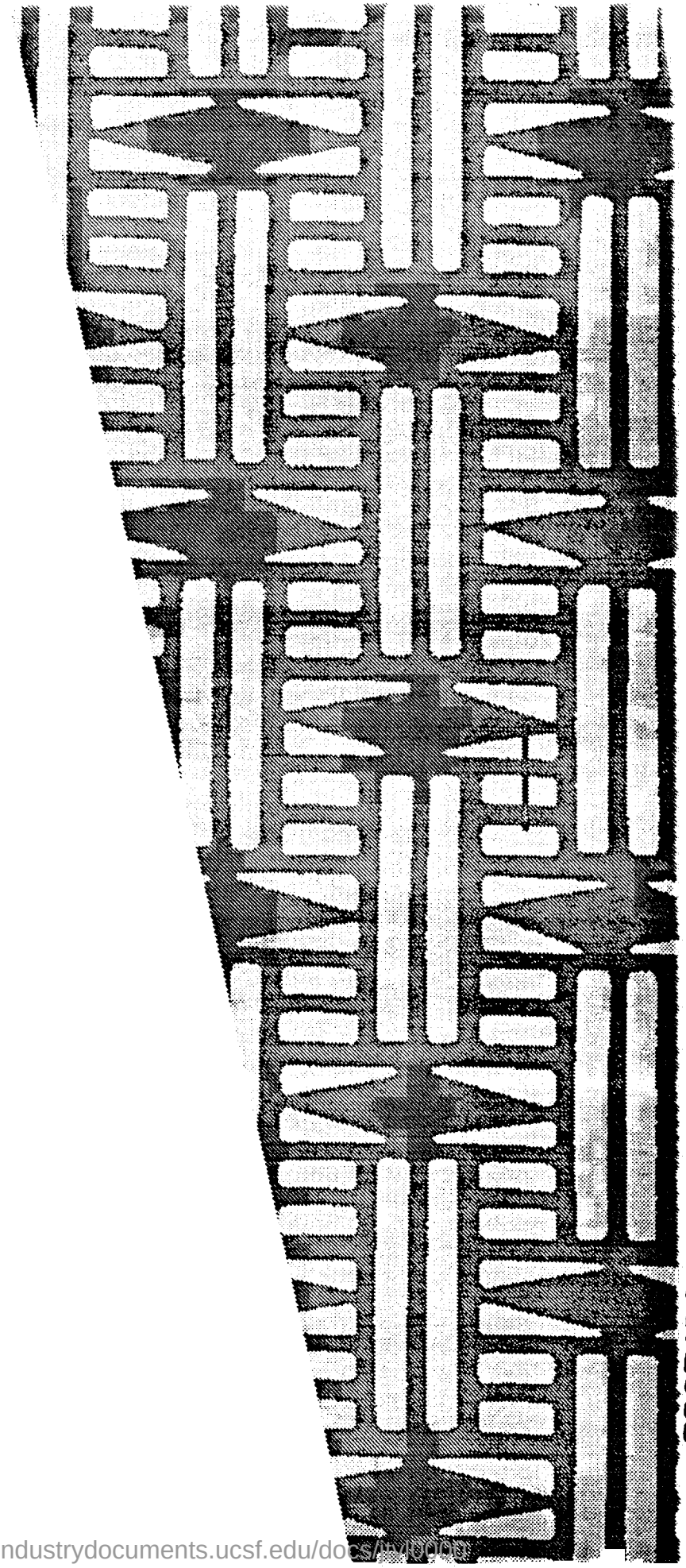

TRDRP

Tobacco-Related Disease Research Program

July 1992

Grants Awarded In

Epidemiology and Behavior and Public Health Research on Tobacco

Office of the President
Vice President-Health Affairs
300 Lakeside Drive, 12th Floor
Oakland, CA 94612-3550
Tel: (510) 987-9870
FAX (510) 835-4740

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Source: https://www.industrydocuments.ucsf.edu/docs/nvjc0000

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- List of Funded Projects
- Abstracts of Funded Projects
- Roster of Study Section Members

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Background
Tobacco-Related Disease Research Program
University of California

In November 1988, California voters approved Proposition 99, the Tobacco Tax and Health Protection Act, which instituted a 25¢-per-pack cigarette surtax. This initiative specified that five percent of the revenue be deposited into a Research Account, to be appropriated for research on tobacco-related disease. The Tobacco-Related Disease Research Program was established by passage of SB 1613 (Chapter 1330 of the Statutes of 1989) in October 1989: "The Legislature hereby requests the University of California to establish a comprehensive grant program to support research efforts related to the prevention, causes, and treatment of tobacco-related diseases" (Section 424.20 of the Health and Safety Code).

Within the Office of the President of the University of California, specific responsibility for administering this research program was assigned to the Vice President—Health Affairs, Cornelius L. Hopper, M.D., who established the Tobacco-Related Disease Research Program (TRDRP). TRDRP has responsibility for the management of all fiscal and programmatic aspects of the grant program, while the Research Administration Office in the Office of the President manages all contractual relationships with institutions other than University of California campuses.

Direction and oversight of TRDRP are provided by a Scientific Advisory Committee which comprises representatives of various institutions with interest in the program. A list of members and the institutions they represent appears at the end of this booklet.

Research funds are available to investigators at all non-profit research institutions in California. Grant applications are peer reviewed by panels of leading investigators drawn from research institutions throughout the country. The evaluation procedure is modeled on the one used by the National Institutes of Health. In 1992, 132 reviewers evaluated applications in the following nine study sections:

Behavioral and Public Health Research on Tobacco
Carcinogenesis
Cardiovascular Disease
Epidemiology
General Biomedical Science
Pulmonary Disease
Tumor Immunology and Therapy
Cancer and Biomedical Science Career Development
Cardiovascular and Pulmonary Disease Career Development

Study sections evaluated the scientific merit of proposals and rated their responsiveness to TRDRP's current research priorities. The Scientific Advisory Committee reviewed these evaluations and recommended funding levels to the UC Vice President—Health Affairs.

In 1992 TRDRP awarded approximately $24 million to investigators at 25 institutions. The 87 grants awarded constituted more than 21 percent of applications received. From July 1990 to date, TRDRP has awarded 376 grants, for a total of approximately $118 million, to investigators at 40 California research institutions. TRDRP issues an annual report to the California Legislature which includes reports of scientific progress on active grants.

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Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

SCIENTIFIC ADVISORY COMMITTEE

MEMBER	REPRESENTING:
Judith Campisi, Ph.D. Division of Cell and Molecular Biology Lawrence Berkeley Laboratory, Bldg. 83 Berkeley, California 94720	Lawrence Berkeley Laboratory
Robert W.P. Cutler, M.D. Medical Center, M-121 Stanford University School of Medicine Stanford, California 94305	Stanford University
Earl J. Freise, Ph.D. Office of Sponsored Research California Institute of Technology Mail Stop 213-6 Pasadena, California 91225	California Institute of Technology
Stephen L. Hansen, M.D. 1744 Alisol Street San Luis Obispo, California 93401	California Medical Association
M. Alfred Haynes, M.D., M.P.H. 29249 Fithridge Road Rancho Palos Verdes, CA 90274	Drew University of Medicine and Science
Lowell Irwin, M.D. 1245 Wilshire Boulevard, Suite 303 Los Angeles, California 90017	American Cancer Society California Division
Dieter Kramsch, M.D. Artherosclerosis Research Institute University of Southern California 2011 Zonal Avenue Los Angeles, California 90033	University of Southern California

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MEMBER	REPRESENTING:
Anthony Moye, Ph.D. Academic Affairs, Resources California State University 400 Golden Shore Drive Long Beach, California 90802	California State University
Nicholas Petrakis, M.D. Department of Epidemiology and Biostatistics Box 0560, HSW 1699 University of California, San Francisco San Francisco, California 94143	University of California
Daniel Steinberg, M.D., Ph.D. Division of Endocrinology and Metabolism Department of Medicine, 0613-D University of California, San Diego 9500 Gilman Drive San Diego, California 92093	American Heart Association California Affiliate
Donald F. Tierney, M.D. Pulmonary and Critical Care Medicine Center for the Health Sciences University of California, Los Angeles 10833 Le Conte Avenue Los Angeles, California 90024	American Lung Association of California
Lawrence Wallack, Dr.P.H. Department of Social and Administrative Health Sciences 516 Warren Hall University of California, Berkeley Berkeley, California 94720	University of California at Berkeley

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Epidemiology

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Epidemiology
Funded Projects

Research Awards

Burns, David M.	Modeling US Lung Cancer Death Rates	University of California, San Diego
Dwyer, James H.	Smoking and HDL Cholesterol in Minority Youth	University of Southern California
London, Stephanie J.	Genetic Markers of Lung Cancer Risk Among Blacks & Whites	University of Southern California
Shaw, Gary M.	Oral Clefts, Candidate Genes, & Parental Tobacco Use	March of Dimes Birth Defects Foundation
Swan, Shanna H.	Hormones and Tobacco: Joint Effects on Reproduction	California Public Health Foundation
Wu-Williams, Anna H.	Smoking and Risk of Proximal Vs. Distal Gastric Cancer	University of Southern California
Wyrobek, Andrew J.	Tobacco Smoke Exposure & Chromosomally Defective Sperm	Lawrence Livermore National Laboratory

New Investigator Awards

Kass, Philip H.	Animal Models of Human Risk from Environmental Tobacco Smoke	University of California, Davis

2023471015

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: BURNS, David M.

ABSTRACT

Modeling U.S. Lung Cancer Death Rates

Title of Research Project (do not exceed 60 spaces)

Cancer Center, UCSD

Department and Institution

This application is a request for three years of funding for a project that was funded for a single year in the last funding cycle to allow demonstration that access to prospective mortality data would be available to the investigators.

Two separate theories on the process of carcinogenesis, the multistage model and the two mutation model, have been used to develop mathematical models that use smoking prevalence data to predict lung cancer death rates. Each of these models appears to fit the lung cancer risk data from a prospective mortality study of smoking and nonsmoking British physicians, but they result in markedly different conclusions about the importance of the pattern of lifetime smoking for lung cancer risk.

We propose:

1. To use detailed US birth cohort data on the prevalence, intensity, and duration of smoking in white males to test which of the two models better predicts US lung cancer death rates.
2. To use data from the American Cancer Society Cancer Prevention Study I (CPS I) to test which of the mathematical models developed using the British Physician study better predicts the lung cancer death rates observed in the CPS I study.
3. To derive new estimates of the parameters of the two models using the CPS I data, and to compare these new estimates to those derived from the British Physician study for their ability to predict US white male lung cancer death rates using US 5 year birth cohort data on the prevalence, intensity, and duration of smoking among white males.
4. To compare the predicted lung cancer death rates using the models with the actual US lung cancer death rates to test whether the change in cigarette composition over time has altered the carcinogenicity of the cigarettes smoked by the US population.
5. To compare the models' predictions of lung cancer death rates for white females and black males (using the birth cohort smoking patterns of black males and white females) to the actual US lung cancer mortality rates for these groups in order to generate an estimate of the fraction of the differences in lung cancer mortality between these groups explained by the differences in their smoking behavior.

2023471016

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: James H. Dwyer, Ph.D.

ABSTRACT

Smoking and HDL Cholesterol in Minority Youth
Title of Research Project (do not exceed 60 spaces)

Department of Preventive Medicine
Institute for Prevention Research
Department and Institution

There is substantial evidence that plasma concentration of cholesterol in high density lipoprotein (HDL-C) is inversely related ("protective") to cardiovascular disease (CVD) risk in whites. There is also some evidence that cigarette smoking is associated with lower HDL-C in whites. These two observations suggest the hypothesis that depressed HDL mediates part of the effect of smoking on CVD risk.

However, several questions remain concerning the observed association between smoking and HDL-C: (1) Some evidence suggests that the association is spurious due to confounding with other behaviors (esp. diet); (2) Some evidence suggests that the association is due primarily to an effect of smoking on HDL_3, rather than the anti-atherogenic HDL_2 sub-fraction; (3) The generalizability to blacks of data from whites on metabolic effects of smoking is challenged by the recent finding that nicotine metabolism may differ between blacks and whites. Also, the only available data on smoking and HDL-C in black youth failed to detect the same association found in white youth; black females who became smokers actually evidenced an increase in HDL-C relative to non-smokers (Bogalusa Heart Study; Freedman, 1986).

It is proposed that the relation between smoking, HDL-C, HDL-C sub-fractions, and related apolipoproteins be investigated longitudinally among a multi-ethnic cohort of high school students followed from the 9th to 11th grades (N=1500). Changes in smoking, lipids, diet, exercise levels, and body composition will be tracked annually. It is hypothesized that becoming a smoker will be associated with a relative reduction in HDL-C among all students, and with a reduction in HDL_2-C and apoA-I in frozen plasma from a sub-sample of black youth (60 who become smokers, matched with 60 who do not).

2023471017

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Stephanie J. London

ABSTRACT

Genetic markers of lung cancer risk among blacks and whites

Title of Research Project (do not exceed 60 spaces)

Dept. of Preventive Medicine, Univ. of Southern California School of Medicine

Department and Institution

Genetic factors are likely to play a significant role in determining lung cancer risk, perhaps by influencing individual response to carcinogens in tobacco smoke and the environment. Various carcinogens in tobacco smoke are activated by cytochrome P450 enzymes. In turn, enzymes such as the glutathione S-transferases are involved in detoxication of these activated metabolites. The genes that code for several cytochrome P450 enzymes and the enzyme glutathione S-transferase 1 are polymorphic and thus might relate to individual variation in susceptibility to lung cancer.

We propose to expand upon our case-control study of the debrisoquine 4-hydroxylase (*CYP2D6*) polymorphism and lung cancer funded by the State of California Tobacco Related Disease Research Program (RT140). Specifically, we will study the relation between lung cancer risk and polymorphisms of the following cytochrome P450 genes: *CYP1A1*, *CYP2A6*, and *CYP2E1*. In addition we will examine the relation between lung cancer risk and the genetic polymorphism of glutathione S-transferase 1 (GST1).

We will also examine differences in these genetic polymorphisms between blacks and whites to gain further insight into the major differences in their lung cancer rates which do not appear to be due to variation in smoking habits.

Analyses for these genetic polymorphisms will be performed on DNA from peripheral blood already being collected on 320 incident lung cancer cases and 640 community controls. Equal numbers of black and white subjects are being enrolled.

2023471018

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Gary M. Shaw, DrPH

ABSTRACT

ORAL CLEFTS, CANDIDATE GENES, AND PARENTAL TOBACCO USE

Title of Research Project (do not exceed 60 spaces)

March of Dimes Birth Defects Foundation

Department and Institution

Most oral cleft birth defects (cleft lip and palate) are thought to result from environmental and genetic causes, or their interactions. Among the environmental causes, several studies have suggested that tobacco smoking during pregnancy increases the risk of delivering an infant with an oral cleft defect. Recently, two studies have found that a genetic variant of a growth factor gene, transforming growth factor-α, occurs 3-4 times more frequently among children with non-familial oral clefts than among controls. No studies have addressed the potential interaction between smoking, clefting, and genetic variation.

The purpose of this proposed study is to investigate such an interaction by analyzing whether women using tobacco products during early pregnancy, or men using tobacco products before conception, have an increased risk of delivering infants with clefts, and whether this risk is affected by genetic variation of a number of growth factor genes known to be involved in embryogenesis of the lip and palate. We propose to accomplish this by extending TRDRP grant 1RT466, a case-control study underway that includes cases with oral cleft defects born in 1987 and 1988 and ascertained by the population-based California Birth Defects Monitoring Program. The extension would increase the case group to 975 infants with oral clefts and 1000 controls by including 1989 births, and provide genotyping data for all of these study subjects. Exposure information will be derived from telephone interviews with mothers of cases and controls. The genotyping would be done using DNA from residual newborn screening blood samples for the cases and controls, obviating the need for phlebotomy. The increased study population would allow us to perform essential subgroup analyses for each type of cleft, for isolated versus non-isolated defects, and for the genotypic data. This unique epidemiologic study will enhance our ability to identify environmental causes of clefts, especially the risk associated with tobacco use, by reducing case misclassification, and will pioneer the study of genetic interaction with environmental factors.

2023471019

Dock

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Shanna Swan, Ph.D.

ABSTRACT

Hormones and Tobacco: Joint Effects on Reproduction

Title of Research Project (do not exceed 60 spaces)

California Department of Health Services

Department and Institution

The purpose of this proposed study is to examine hormonal mechanisms for possible relationships between exposure to tobacco smoke (active and passive) and two female reproductive endpoints; subfecundability and fetal loss. Several lines of evidence suggest that smoking is anti-estrogenic, perhaps by altering steroid hormone production or metabolism, thus potentially impacting female reproductive health. These questions will be explored in the Reproductice Health Study which includes 404 married women who were noncontracepting or using barrier methods. Women provided baseline questionnaires, daily diaries and urine samples for 1-8 menstrual cycles (average 4.6). During this period, women reported 53 pregnancies, and subclinical pregnancies will be identified. Daily measurements of urinary metabolites of estrogen (E1C) and progesterone (PdG), as well as human chorionic gonadotropin (hCG) on 15 days of each cycle, are currently available on 250 women. Results from these, and the remaining assays for which funding is requested, will provide hormone profiles and data on subclinical pregnancies. We propose to reinterview women after two years to identify additional pregnancies and changes in smoking, contraception and other factors. In addition, we seek funding for three serial urinary assays for cotinine per subject which will detect changes in exposure to cigarette smoking and environmental tobacco smoke. These assays will provide an objective measure which will be compared to self reported exposures. We will examine a woman's hormone profile and tobacco exposure in relation to her reproductive experience during the 26-30 month study period. The first stage in the analysis will examine tobacco exposure in relation to ovarian function and luteal phase defects. The second stage will examine tobacco exposure in relation to fecundability and fetal loss, independent of hormonal function. In the third stage, hormonal function will be studied in relationship to fecundability and fetal loss, independent of tobacco exposure. We will then evaluate whether tobacco-related changes in hormonal parameters observed in the first stage explain altered risk of subfecundability or fetal loss in tobacco exposed women. While epidemiologic evidence suggests a relationship between (active) smoking and estrogen level, fecundability and spontaneous abortion, the strength of these associations is uncertain. Passive tobacco exposure has not been widely studied in relation to these endpoints although we found a positive association in a recent case-control study of spontaneous abortion. Abnormal steroid profiles have been linked to both infertility and habitual spontaneous abortion, but these results are based on small clinic populations. The proposed study will allow us to link laboratory data on steroid and cotinine levels to epidemiologic data on time to conception and spontaneous abortion, thus providing an opportunity to explore the hypothesis that tobacco exposure alters fecundability and risk of pregnancy loss via alteration of steroid hormones. This study will also provide distributions of urinary hormone profiles and tobacco exposures for a nonclinic, population-based sample of women which are currently unavailable.

2023471020

Door

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Anna H. Wu-Williams

ABSTRACT

Smoking and Risk of Proximal Vs. Distal Gastric Cancer

Title of Research Project (do not exceed 60 spaces)

Department of Preventive Medicine, University of Southern California

Department and Institution

Although gastric cancer incidence overall has declined in the U.S. during the past 50 years, the incidence of adenocarcinoma of the gastric cardia and lower esophagus has recently substantially increased. Compared to gastric and esophageal cancer overall, adenocarcinomas of the gastric cardia and lower esophagus (referred to as proximal gastric adenocarcinomas) are characterized by a high male to female ratio and are relatively more common in Whites than Blacks.

Causes for the increase of proximal gastric adenocarcinomas are not known. The irritant properties of tobacco smoke may damage the gastric mucosa and exert a direct effect on gastric cancer or smoking may have an indirect role through its effects on gastrointestinal physiology. Smoking may also modify the effect of other suspected risk factors of stomach cancer which include alcohol, diet, various benign pathologic conditions of the stomach, esophagus or duodenum and use of specific medications such as H_2-blockers. Recent studies suggest that Helicobacter pylori infection may have an important role in gastric carcinogenesis but the environmental factors which increase the risk of gastric cancer among persons with the infection have not been identified.

We propose to conduct a population-based case-control study including Blacks, Whites, and Latinos to contrast risk factors for proximal gastric adenocarcinomas with those for distal stomach cancers. This study will evaluate the role of tobacco smoking, alcohol use, dietary factors, prior benign conditions of the stomach and esophagus, and use of certain categories of drugs in the etiology of proximal and distal gastric adenocarcinomas. This study which will enroll 665 cases and 665 controls will be the largest analytic study to date to examine risk factors of gastric cancers by subsite.

2023471021

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Wyrobek, Andrew J., Ph.D.

ABSTRACT

Tobacco smoke exposure and chromosoomally defective sperm

Title of Research Project (do not exceed 60 spaces)

Lawrence Livermore National Laboratory

Department and Institution

The objective of this research is to determine if cigarette smoking and exposure to environmetal tobacco smoke induces chromosomal damage in human sperm using a new sensitive method for detecting aneuploid sperm. Sperm carrying chromosomal aneuploidies are detected by fluorescence *in situ* hybridization with chromosome-specific repetitive-sequence DNA probes. This method was developed at our laboratory and recently validated using the human-sperm/ hamster-egg cytogenetic system and human birth data. Cohybridization with multiple probes each tagged with a fluorescent dye of a different color will be used to detect several types of aneuploidies simultaneously in the same preparations: eg., 1-1, X-X, Y-Y and X-Y. This survey includes aneuploidies of autosomes as well as sex chromosomes. Fertilization with sperm carrying Y-Y and X-Y aneuploidies are predicted to yield liveborn aneuploid offspring (XYY and XXY, Klinefelter syndrome). These sperm aneuploidies, therefore, are considered biomarkers for paternally inherited genetic defects.

This research will utilize semen samples already obtained from a well characterized population of approximately 160 "normal" men. The men are partners of women enrolled in the larger Pregnancy Outcome Study conducted by the California Department of Health Services, which recruited 500 women from Kaiser Permanente Medical Center in Santa Clara, California. Husbands provided two semen samples during the menses of the first two months that their wives were enrolled. Information being obtained on this cohort (under separate funding) includes (a) tobacco smoke exposure assessment based on four different tobacco exposure indicators, (b) detailed questionnaire data regarding occupational, medical, personal, and lifestyle factors, and (c) computer-based measurements of sperm morphometry and motility performed on the same semen samples. Funding is requested to measure the fraction of aneuploid sperm in semen samples from this cohort and to perform statistical analyses to determine (a) the effects of active smoking, (b) the effects of exposure to environmental tobacco smoke and (c) the dose-response relationship between sperm aneuploidy and exposure level of active smoke. This study has an 80% power to detect a ~15% increase in mean fraction of aneuploid sperm in smokers compared with non-exposed controls.

This research will yield pivotal information on the question of whether cigarette smoking induces chromosomal damage in the sperm of active smokers and men exposed to environmental tobacco smoke.

2023471022

DOOR

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

Principal Investigator: Kass, Philip H.

ABSTRACT

Animal Models of Human Risk From Environmental Tobacco Smoke

Title of Research Project (do not exceed 60 spaces)

Department of Epidemiology and Preventive Medicine, School of Vet. Med., U.C. Davis

Department and Institution

This research will provide epidemiologic evidence concerning the association between environmental tobacco smoke (ETS) and lung cancer. We will take the novel approach of studying pet animals because household pets have greater exposures to the indoor home environment and because animals develop cancer in a much shorter time span than do humans. Dogs and cats (as well as humans) develop histologically similar forms of lung cancer, but the etiology of this cancer in non-experimental animals is unknown. Since the association between ETS and lung cancer in people remains controversial, dogs and cats represent natural *in vivo* and *in situ* models. The goals of this study are thus to:

1. Determine what association exists between lung cancer and ETS in dogs and cats.
2. Demonstrate the use of dogs and cats as sentinels of environmental health hazards in the home.

A prospective case-control study will be undertaken in California and surrounding states using a disease registry established by a veterinary pathology laboratory (California Veterinary Diagnostics, Inc.), which provides services to most veterinarians in northern California. Cases will include animals with a pathologic diagnosis of primary pulmonary carcinoma. Controls will include dogs and cats with pathologic diagnoses of splenic hematomas, reactive lymph nodes, and lipomas (conditions which are not known to be etiologically related to tobacco smoke). Owners of the pets will be interviewed and questioned about environmental tobacco smoke and other potential confounders (including other possible cancer determinants) in the home environment. These include pesticide and herbicide use, diet, and non-tobacco combustible substances released by appliances inside the home. Measures of exposures will be statistically analyzed using multivariate regression methods. If environmental tobacco smoke is found to be associated with canine or feline lung cancer, then the results add support for the causal hypothesis of ETS and human lung cancer.

2023471023

DOOR

Source: https://www.industrydocuments.ucsf.edu/docs/jtvl0000

TOBACCO-RELATED DISEASE RESEARCH PROGRAM

Epidemiology Study Section

Roster

Chairman

Dimitrios Trichopoulos, M.D.
Harvard School of Public Health
Department of Epidemiology
677 Huntington Avenue
Boston, MA 02115

Members

John Baron, M.D.
Dartmouth Medical School
Strasenburgh Hall, Apartment B
Hinman Box 7927
Hanover, NH 03756

Graham A. Colditz, M.D., Ph.D.
Harvard University
Channing Lab
180 Longwood Avenue
Boston, MA 02115

William J. Blot, Ph.D.
National Cancer Institute
Division of Cancer Etiology
6130 Executive Boulevard
Executive Plaza North 431
Rockville, MD 20592

Katherine Detre, M.D., Ph.D.
University of Pittsburgh
School of Public Health
Department of Epidemiology
A531 Crabtree Hall
Pittsburgh, PA 15261

Michael Bracken, Ph.D.
Yale School of Medicine
Dept. of Epidemiology & Public Health
60 College Street
New Haven, CT 06510

Dwight T. Janerich, D.D.S., M.P.H.
University of Utah
Utah Cancer Center
Health Sciences Center, Room 2C110
50 North Medical Drive
Salt Lake City, UT 84132

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Juliette S. Kendrick, M.D.
Centers for Disease Control
Cntr. Chronic Disease Prev. & Control
1600 Clifton Road (K23)
Atlanta, GA 30333

Rick Severson, Ph.D.
University of Minnesota
Division of Pediatric Oncology
420 Delaware Street, S.E.
Room D557 Mayo, Box 422 UMHC
Minneapolis, MN 55455

Michael Lebowitz, Ph.D.
University of Arizona
Department of Medicine
1501 N Campbell Avenue
Room 2332
Tucson, AZ 85724

Thomas Vaughn, M.D., Ph.D.
Fred Hutchinson Cancer Research Center
Program in Epidemiology, MP-474
1124 Columbia Street
Seattle, WA 98104

Thomas Rohan, M.D., Ph.D.
University of Toronto
NCIC Epidemiology Unit
McMurrich Building, Third Floor
12 Queens Park Crescent West
M5S 1A8
Toronto, Canada

Cosette Wheeler, Ph.D.
University of New Mexico
Cancer Center
900 Camino de Salud
Albuquerque, NM 87131

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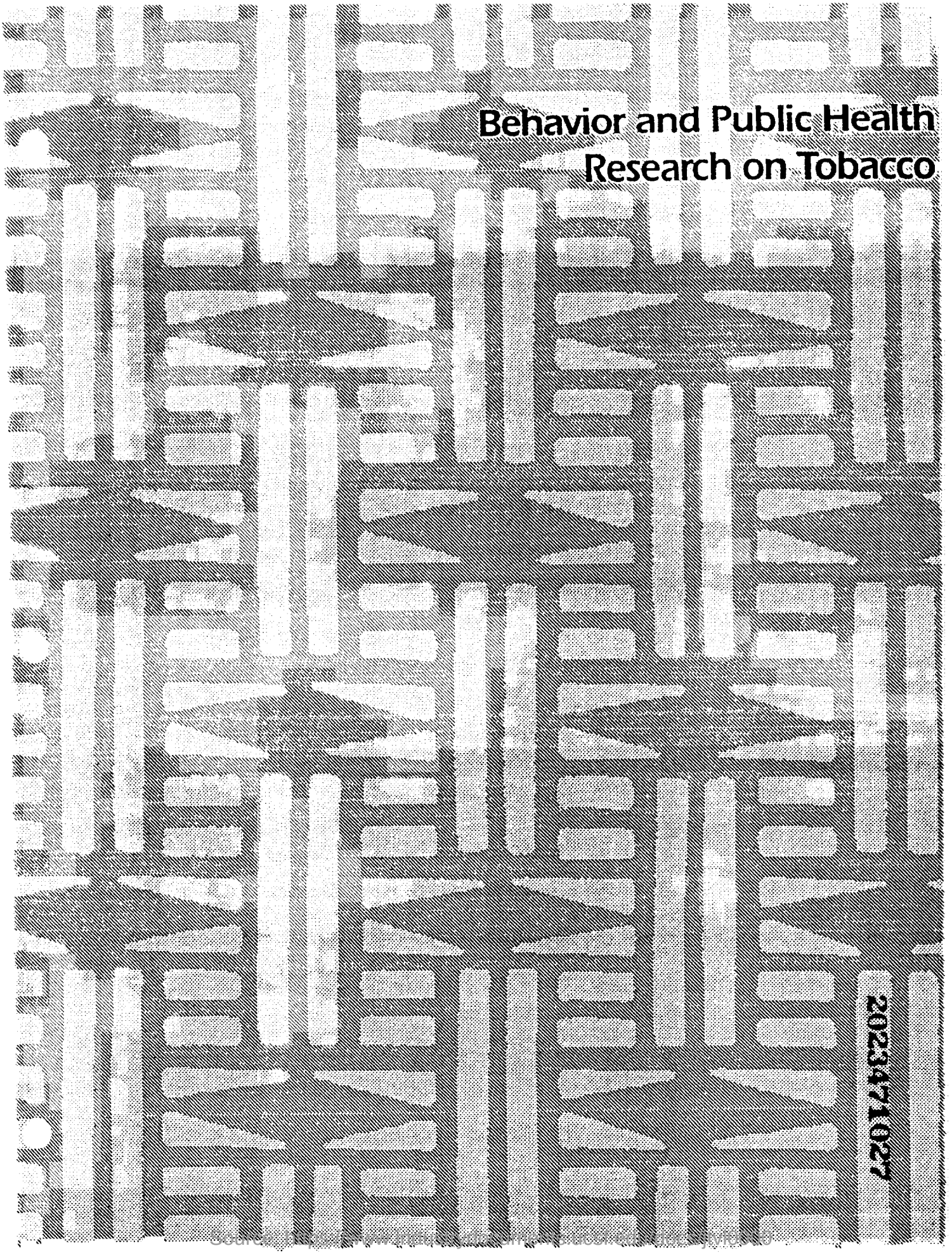
Behavior and Public Health Research on Tobacco



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